ORIGINAL ARTICLE

ROLE OF PREEMPTIVE NALBUPHINE IN REDUCING THE USE OF POSTOPERATIVE ANALGESICS FOR PAIN AND TRISMUS AFTER SURGICAL EXTRACTION OF IMPACTED MANDIBULAR THIRD MOLAR

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Background: To underscore the significance of risk mitigation strategies associated with the surgical extraction of impacted mandibular third molar, a comprehensive understanding of postoperative complications is essential. Such primary complications include the possibilities of postoperative pain, trismus, infection, nerve injury, excessive hemorrhage, delayed healing and inadvertent damage to neighboring structures. This study investigates the impact of preemptive intravenous nalbuphine administration on postoperative pain and trismus management following surgical extraction of impacted mandibular third molars. **Methods**: A total of 310 patients were divided into two groups, with Group I (n=156) receiving nalbuphine and Group II (n=154) receiving a placebo. Postoperative pain scores (on visual analog scale), analgesic usage, and maximum mouth opening (MMO) were evaluated. **Results**: The patients aged 15–40 year in both groups, with mean = 27.2±7.0 and 28.1±8.3 years for Group I and II, respectively (p>0.05). The mean postoperative pain in Group II was significantly higher (p<0.0001) than in Group I, with pain score restricted to 2–6 in Group I, compared to 2–10 in Group II. Patients in Group II consumed the postoperative analgesics for a significantly longer duration (p<0.0001) than patients in Group I. The MMO data showed that the number of patients with mouth opening less than 30 cm was significantly smaller (p<0.0001) in Group I as compared to Group II (i.e., 42 versus 114). **Conclusions**: These results underscore the therapeutic potential of preemptive nalbuphine in enhancing patient comfort and recovery after impacted mandibular third molar extraction, providing a valuable framework for optimizing patient outcomes.

Keywords: Third molar; Maximum mouth opening; Visual analog scale; Analgesics

Citation: Khattak YR, Qazafi M, Islam M, Iqbal A, Khattak JU, Shah K, Mushtaq. Role of preemptive Nalbuphine in reducing the use of postoperative analgesics for pain and trismus management after surgical extraction of impacted mandibular third molar. J Ayub Med Coll Abbottabad 2025;37(1):85–90.

DOI: 10.55519/JAMC-01-12971

INTRODUCTION

To underscore the significance of risk mitigation strategies associated with the surgical extraction of impacted mandibular third molar, a comprehensive understanding of postoperative complications is essential. Such primary complications include the possibilities of postoperative pain, trismus, infection, nerve injury, excessive hemorrhage, delayed healing, and inadvertent damage to neighboring structures.[1] These complications, albeit infrequent, necessitate meticulous attention during preoperative planning and intraoperative execution.

Clinical strategies for the management of postoperative complications following surgical extraction of impacted mandibular third molars involve a systematic and evidence-based approach. Regular postoperative follow-ups allow for early detection and intervention, reducing the risk of complications. For example, the timely administration of appropriate antibiotics can effectively combat infections, while encouraging gentle jaw exercises and warm compresses can alleviate trismus. Likewise, analgesics and anti-inflammatory medications can effectively manage pain and swelling. Moreover, preemptive analgesics may have a role in reducing postoperative pain, as these agents target pain pathways and reduce sensitization of the central and peripheral nervous systems.[2] By addressing pain before it becomes established, the patients are provided with superior pain relief and significantly reduced discomfort during the postoperative period. Furthermore, preemptive analgesics lead to a decreased demand for rescue pain medication post-surgery, minimizing the risk of over-reliance on opioids and

their associated adverse effects. Preemptive analgesics can also help suppress the postsurgical inflammatory cascade, further contributing to reduced pain and swelling. Also, by offering preemptive analgesia, the overall comfort of patients is enhanced. Subsequently, the patients are encouraged for better adherence to postoperative care instructions, facilitating a smoother recovery process of the patient. Specifically, pain signals originate from nociceptors in response to inflammation or tissue damage. The pain may originate from abnormal nerve signaling during neuropathic conditions. Such signals are transmitted via the dorsal horn of the spinal cord, where primary afferent neurons synapse with secondary neurons. Pain perception occurs in the brain, involving areas like the thalamus and cortex. Analgesics achieve pain relief by interfering with signal generation, transmission, or perception, targeting molecular mechanisms like enzyme inhibition, ion channel modulation, and receptor activation to disrupt pain signaling at various levels.

Considering each patient's medical history, allergies, and risk factors is essential when selecting preemptive analgesics. For example, non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing inflammation, pain, and swelling and can be used as the first line of analgesics due to their proven efficacy. However, NSAIDs may cause stomach upset and ulcers, especially with prolonged use. Other side effects of NSAIDs include headaches, dizziness, and, rarely causing liver and kidney problems. Acetaminophen is another effective and well-tolerated analgesic in managing mild to moderate pain. However, it lacks anti-inflammatory properties. Likewise, opioids (e.g., codeine, tramadol, hydrocodone) are potent agents for pain relief, especially for severe postoperative pain. The common side effects of opioids include nausea, constipation, dizziness, and sedation. In addition to these analgesics, nalbuphine has also been reported as an effective preemptive analgesic agent in oral surgery[3], labor pain, pruritus, opioid-induced urinary retention and respiratory depression, laparoscopic total hysterectomy[4,5], with high potency in the management of moderate to severe pain[6]. This study aimed to assess the preemptive intravenous nalbuphine in reducing postoperative analgesics in the pain and trismus management after surgical extraction of impacted mandibular third molar.

MATERIAL AND METHODS

The Research and Ethical Committee of Hayatabad Medical Complex (HMC), Peshawar approved (approval number 579/HEC/B&PSC/2021) to conduct this study at the Department of Oral and Maxillofacial surgery, HMC, Peshawar. All patients were briefed about their voluntary participation in this study before signing the written consent. Patients undergoing surgical extraction of impacted mandibular third molar under local anesthesia were selected and randomly divided in two groups: first group of patients (Group I) was intravenously injected 10 milligram nalbuphine 30 minutes before the tooth extraction, while second group of patients (Group II) was given placebo (i.e., normal saline without any analgesics). Patients presenting with odontogenic cysts/tumors, metallic restorations, history of tooth extractions, hypersensitivity to nalbuphine and comorbidities (e.g., pregnancy, diabetes, psychiatric disorders or immune deficiency) were excluded from this study.

Clinical variables, including the patient's age, gender, duration of using postoperative analgesics, severity of pain on a visual analog scale and postoperative maximum mouth opening (MMO) were recorded for each patient. Data manipulation and analysis was carried out in SPSS, while data plotting and presentation were performed in Origin pro.

RESULTS

In this study, 310 patients were divided into two groups. Group I (n=156) received preemptive intravenous nalbuphine, while Group II (n=154) received a placebo. Patient's demographics were analyzed using fundamental descriptive statistics. Specifically, gender distribution (Table-1) demonstrated slight differences between the groups (1.17 versus 1.75 male-to-female ratio in Group I and II, respectively), but these disparities were not statistically significant (chi-square test, $p>0.05$). The age range for both Group I and Group II stood at 15–40 years, highlighting the robustness of the study's age representation. The mean age (± standard deviation) of patients in Group I was 27.2±7.0 years, while Group II displayed a mean age of 28.1±8.3 years, further bolstering the rigor of this study. Furthermore, the data showcased that the median age of patients in Group I was slightly lower than that of Group II (i.e., 26 versus 27 years).

As a prerequisite for the postoperative use of analgesics, the gender-specific analysis, presented in Table 2, revealed no correlation between pain scores and patient gender for both Group I ($p=0.063$) and Group II ($p=0.17$).

Evaluation of the postoperative pain experienced by patients, determined using the visual analog scale, is presented in Table 2, which reveals notable differences in postoperative pain between the two groups. Specifically, while both groups exhibit

pain scores that conform to normal distributions, Group II displays a discernible shift towards higher pain scores, signifying that the mean pain experienced by patients in Group II surpasses that of Group I. Moreover, pain scores in Group I are confined within the 2–6 range, in contrast to the wider range of 2–10 in Group II. The chi-square test showed that the number of patients with moderate pain was statistically higher (p<0.0001) in Group I as compared to Group II. These findings collectively suggest the efficacy of preemptive nalbuphine administration in mitigating postoperative pain after the surgical extraction of impacted mandibular third molars.

The utilization of postoperative analgesics by patients in both groups was monitored for a duration of up to postoperative day 10. The comparison of this analysis for both groups, in their entirety and individually stratified by gender, is illustrated in Figure 1 and 2, respectively. Notably, patients in Group II exhibited a prolonged usage of postoperative analgesics compared to Group I, a pattern consistent across both male and female patients. In Group I, approximately 90% of patients employed analgesics until postoperative day 6, whereas this number dropped to approximately 58% in Group II. Conversely, only around 10% of patients in Group I continued using analgesics beyond 6 days, a significantly smaller figure compared to the approximately 42% observed in Group II. Remarkably, none of the patients in Group I used analgesics for more than 8 days, whereas 20% of patients in Group II did so. Moreover, male patients in Group I used analgesics until postoperative day 7, whereas those in Group II extended this usage until postoperative day 10. Female patients displayed a similar trend.

To statistically analyze this, we categorized the use of postoperative analgesics into two classes: patients using analgesics up to postoperative day 5 were termed "single dose patients," and those using analgesics for more than five postoperative days were termed "double dose patients." Employing the chi-square test, we found a notably higher number of single dose patients in Group I, signifying statistical significance (p<0.001) in comparison to Group II.

We assessed the maximum mouth opening (MMO) of all patients on postoperative day 8 using the standard method, which involved measuring the distance between the incisors of the mandible and maxilla. Patients were classified into two groups based on their MMO outcomes, using a cutoff value of 30 cm. Patients achieving a MMO of less than 30 cm comprised one group, while those achieving 30 cm or more were categorized in another group. Figure 3 presents a quantitative comparison of the postoperative MMO for patients in both groups. The number of patients with a MMO less than 30 cm was significantly lower in Group I compared to Group II (42 versus 114: p<0.0001). Conversely, Group I exhibited a greater number of patients with a MMO exceeding 30 cm compared to Group II. These findings suggest that the preemptive administration of nalbuphine appears to effectively facilitate mouth opening following surgical extraction of the mandibular third molar, in contrast to the placebo treatment (normal saline). This enhancement in mouth opening could be attributed to reduced postoperative pain.

This study examined the relationship between postoperative pain and MMO in patients from Group I and Group II (Table-3). For Group II, there was a noticeable trend: as pain scores increased (from 2 to 6 and beyond), the percentage of patients achieving mouth openings beyond 30 cm decreased (from 100–0%). In Group I, a significant drop in mouth opening capacity was observed from 78–23% as pain scores increased from 5 to 6. Notably, patients with minor pain (pain score 2) in Group I could achieve mouth openings beyond 30 cm. These observations support the efficacy of preemptive nalbuphine administration in controlling postoperative pain and enhancing mouth opening. Statistical analysis confirmed a significant correlation between MMO and pain for both Group I (p<0.0001) and Group II (p<0.001).

Table-1: Age and gender distribution of the patients in the two groups

	Group I (Nalbuphine)			Group II (Placebo)		
	Male	Female	Total	Male	Female	Total
Number of patients	84	72	156	98	56	154
Age range*	18-40	16-38	15-40	15-64	18-48	15-64
Mean age	26.5	28.0	27.2	27.5	29.2	28.1
SD	7.0	6.2	6.6	8.3	8.3	8.3
Median age	24.5	26	26	26	28	27

*Age is given in years

Table-2: Postoperative pain on visual analog scale for the patients in the two groups

Pain score	Group I (Nalbuphine)	Group II (Placebo)
1	0	0
2	21	8
3	33	17
4	57	36
5	27	47
6	18	28
7		11
8		4
9		1
10		2

Table-3: Relation of the postoperative MMO and pain for the patients in the two groups

Pain	Maximum mouth opening			
	Group I (Nalbuphine)		Group II (Placebo)	
	<30 cm	≥30 cm	<30 cm	≥30 cm
2	0	21 (100%)	0	8 (100%)
3	9 (27%)	24 (73%)	5 (38%)	13 (62%)
4	15 (26%)	42 (74%)	23 (66%)	12 (34%)
5	6 (22%)	21 (78%)	46 (98%)	1 (2%)
6	12 (77%)	6 (23%)	28 (100%)	0
7			11 (100%)	
8			4 (100%)	
9			1 (100%)	
10			2 (100%)	
Total	42	114	120	34

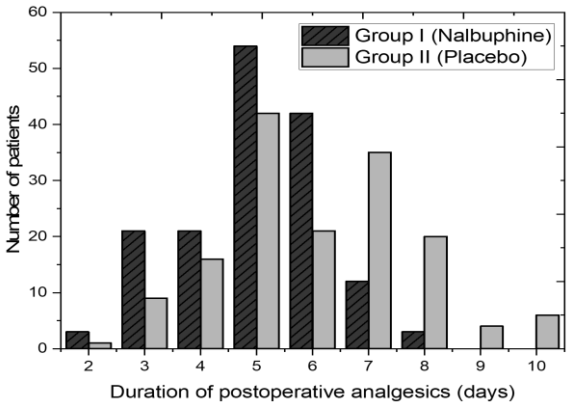

Figure-1: Utilization of postoperative analgesics by patients in both groups

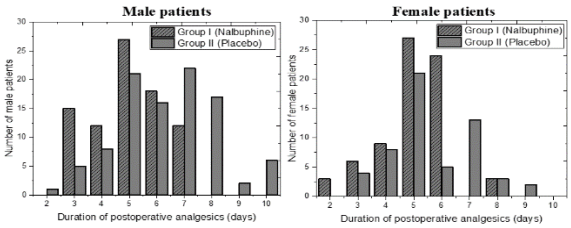

Figure-2: Utilization of postoperative analgesics by patients in both groups individually stratified by gender

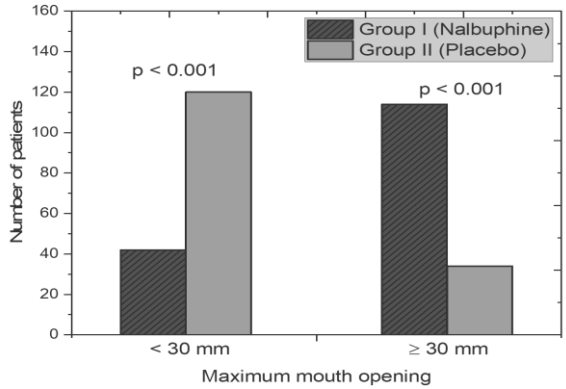

Figure-3: Comparison of postoperative maximum mouth opening of the patients in the two groups

DISCUSSION

Nalbuphine, an opioid analgesic, is widely employed for managing acute and chronic pain. Its analgesic effect involves the inhibition of both pre- and post-synaptic channels. Pre-synaptically, it hampers calcium channels on nociceptive afferent nerves, impeding the release of substance P and glutamate, thus dampening nociception. Post-synaptically, it activates potassium channels, hyperpolarizing cell membranes and elevating the threshold for action potential generation, ultimately hindering nociceptive transmission. Opioid-induced analgesia is mediated by kappa, mu, and delta receptors, exerting effects both at spinal and supraspinal levels.[7,8] Nalbuphine reaches peak serum level after 5 min and the action ranges from 2 to 6 h.[21] Nalbuphine is metabolized in the liver, showing significant potency at the μ receptor.

Pain relief with the use of nalbuphine in preemptive settings has been attributed to its role in modulating nociceptive pathways. In particular, nalbuphine is involved in blocking κ-opioid receptors (KOR) of the central nervous system (i.e., spinal cord). This activation inhibits the release of excitatory neurotransmitters such as glutamate and substance P, reducing the transmission of pain signals along ascending pathways. Simultaneously, nalbuphine exhibits antagonist activity at μ-opioid receptors (MOR), which minimizes side effects like respiratory depression while preserving analgesic efficacy.

At the molecular level, nalbuphine and its metabolites facilitate analgesia by activating KOR, which opens potassium channels and inhibits calcium channels in neurons, leading to hyperpolarization and decreased neuronal excitability. This mechanism suppresses acute nociceptive signals and prevents the amplification of pain during tissue injury or inflammation. By intervening early in the pain cascade, nalbuphine effectively reduces postoperative opioid requirements and mitigates the risk of adverse effects, making it a valuable option for preemptive pain management.

The analgesic effects of nalbuphine in pain relief are consistent across a multitude of conditions.[24] This study found that the patients in Group II (given placebo), both male and female, consumed postoperative analgesics for longer duration (up to postoperative day 10) than the patients in Group I (given nalbuphine), where the analgesics were consumed up to postoperative day 7. These findings indicate the benefits of preemptive nalbuphine administration, in terms of reduction in the postoperative consumption of analgesic agents. It is assumed that the preemptive

nalbuphine would remain in the plasma for an approximate time duration of five times the half-life of the drug, playing its role in controlling the postoperative pain.[9] After surgical removal of the mandibular third molar, the patients in both groups received the same analgesic agent in similar dose, which established that the only difference between the two groups was the preemptive nalbuphine dose.

Moreover, the preemptive nalbuphine may also have a role in diminishing the painful sensation at the end of anesthesia, which is critically important as the patient is unable to take medication due to his transit phase.[10] Previous studies have investigated other opioids for the management of postsurgical pain, including codeine (3-methylmorphine)[11], which demonstrated relief against immediate postoperative pain and delayed the initial onset of pain[12]. Oxycodone, when combined with ibuprofen illustrated superior analgesic efficacy to control pain after third molar extraction, compared with other combinations.[13]

Quantitative analysis of postoperative MMO in the two groups unveiled a marked difference, with Group I exhibiting notably fewer patients with MMO below 30 cm compared to Group II (42 vs. 114). This suggests the potential efficacy of preemptive nalbuphine administration in enhancing mouth opening after mandibular third molar extraction.[14] Several factors influence postoperative mouth opening, encompassing mandibular shelf development stage, surgical approach specifics (such as temporalis tendon sectioning and buccal/distal bone removal), age (>24 years), gender (less frequent in males), oral hygiene, smoking, and surgeon proficiency.[15,16] Ostectomy and mucoperiosteal flap elevation during surgery augment vulnerability to postoperative complications.[17]

Exploring the correlation between postoperative pain and MMO revealed a trend in Group II where the percentage of patients capable of exceeding 30 cm MMO declined from 100% to 0% with increasing pain score (from 2 to 6 and beyond) (Figure-3). While Group I showed no explicit trend, this aligns with earlier research indicating a strong statistical link between pain and reduced mouth opening following impacted mandibular third molar removal.[18] Muscle and fiber damage resulting from extraction likely contributes to pain during mouth opening, particularly in full extension attempts. Postoperative mandibular movement is also constrained by muscle damage.[18] Additionally, other factors significantly influence mouth opening post-surgery. For instance, patients with poor oral hygiene experience heightened pain throughout the postoperative period and require increased analgesic consumption within the initial 48 hours.[19]

CONCLUSIONS

This study rigorously examined the effects of preemptive intravenous nalbuphine on postoperative pain and trismus management following surgical extraction of impacted mandibular third molars. The findings clearly demonstrate the efficacy of nalbuphine in attenuating postoperative pain, reducing analgesic usage, and enhancing mouth opening. This study contributes valuable insights into improving patient care by underscoring the significance of preemptive nalbuphine administration for optimizing patient outcomes in this clinical context.

AUTHORS' CONTRIBUTION

YRK, MQ, MI, MM: Conceptualization. YRK, MQ, MM: Data curation. YRK, MI, KS, MM: Formal analysis. YRK, KS, MM: Investigation, Methodology, project administration, supervision. MI, AI, JUK: Validation. AI, JUK, KS: Visualization. YRK, MQ, MI, AI, JUK, KS, MM: Write-up, draft, review, editing.

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Submitted: February 19, 2924	*Revised: November 20, 2024*	*Accepted: December 11, 2024*

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